AMENDMENTS TO THE CLAIMS

1. (original): A method of preparing controlled release microspheres comprising the steps of:

(a) forming an emulsion comprising an aqueous dispersed phase, said dispersed phase comprising:

a polymer capable of forming a hydrogel,

a bioactive protein, and

water,

and subsequently

(b) crosslinking the polymer physically or chemically to form a hydrogel;

wherein the aqueous dispersed phase is substantially free from insoluble aggregates of said bioactive protein.

2. (original): A method of preparing controlled release microspheres comprising the steps of:

(a) providing a first aqueous phase comprising a polymer capable of forming a hydrogel, a bioactive protein, and water;

(b) providing a second aqueous phase comprising a compound which is capable of phase separation when combined with the polymer capable of forming a hydrogel, and water;

(c) forming an emulsion by dispersing the first aqueous phase in the second aqueous phase; and subsequently

(d) crosslinking the polymer capable of forming a hydrogel physically or chemically to form a hydrogel;

wherein the water content of the second aqueous phase is at least at approximate equilibrium with the water content of the first aqueous phase.

3. (currently amended): A method of preparing controlled release microspheres comprising the steps of:

(a) providing an aqueous phase having a temperature T_1, said phase comprising an amount of:

a bioactive protein;

a polymer capable of forming a hydrogel;

a compound which is capable of phase separation when combined with the polymer capable of forming a hydrogel; and

water;

wherein the amounts are selected to yield an aqueous single phase system at T_1, but a two-phase system at a temperature T_2, [[and]] wherein T_2 is lower than T_1;

(b) cooling the aqueous single phase system provided in step (a) from T_1 to T_2, thereby inducing phase separation and the formation of an emulsion; and subsequently

(c) crosslinking the polymer capable of forming a hydrogel physically or chemically to form a hydrogel.

4. (currently amended): The method of ~~any one of the preceding claims~~ claim 1, wherein the polymer capable of forming a hydrogel is a prepolymer.

5. (currently amended): The method of ~~any one of the preceding claims~~ claim 1, wherein the polymer capable of forming a hydrogel is capable of being physically crosslinked by ~~crystallisation~~ crystallization or stereocomplex formation.

6. (currently amended): The method of ~~any one of the preceding claims~~ claim 1, wherein the polymer capable of forming a hydrogel is a polysaccharide or modified polysaccharide, and preferably a modified dextran.

7. (currently amended): The method of claim 6, wherein the polymer capable of forming a hydrogel is selected from the group consisting of dextran hydroxyethylmethacrylate (dexHEMA), dextran hydroxypropylmethacrylate (dexHPMA), dextran hydroxypropylmethacrylamide (dexHPMAm), and dextran hydroxyethylmethacrylamide (dexHEMAm).

8. (currently amended): The method of ~~any of the preceding claims~~ claim 1, wherein the bioactive protein has a solubility of less than about 10 wt.-% in water or physiological buffer solution at room temperature.

9. (currently amended): The method of ~~any of the preceding claims~~ claim 1, wherein the bioactive protein is selected from the group consisting of insulin, epoetin-alfa, epoetin-beta, calcitonin, heparin, IFN(interferon)-alfa-2a, IFN-alfa-2b, PEG-IFN-alfa, IFN-alfacon-1, IFN-beta, IFN-beta-1a, IFN-beta-1a, IFN-beta-1b, IFN-gamma-1b, somatropin, follitropin, menotropin, leuprolide, goserelin, buserelin, triptorelin, filgrastim (G-CSF), lenograstim (G-CSF), ~~sargrarmostim~~ sargramostim (GM-CSF), PEG-G-CSF, interleukins, blood clotting factors such as factor VIII and factor IX, nadroparin, dalteparin, tinzaparin, certoparin, reviparin, tirofiban, octreotide, antigens, and monoclonal antibodies.

10. (currently amended): The method of ~~any of the preceding claims~~ claim 1, wherein the aqueous phase which comprises the bioactive protein also comprises an excipient which is capable of reducing the aggregation of the bioactive protein.

11. (original): The method of claim 10, wherein the excipient is selected from the group consisting of surfactants, sugars, sugar alcohols, chaotropic agents, antioxidants, amino acids, and inorganic salts.

12. (currently amended): The method of ~~any of the preceding claims~~ claim 1, wherein the step of crosslinking the polymer capable of forming a hydrogel is conducted within about 15 minutes after the formation of the emulsion.

13. (currently amended): The method of ~~any of the preceding claims~~ claim 1, wherein the step of forming an emulsion is conducted as a continuous process.

14. (currently amended): The method of ~~any of the preceding claims~~ claim 1, further comprising any of the following steps:

(a) collecting the microspheres;

(b) purifying the microspheres; and/or

(c) drying the microspheres.

15. (currently amended): The method of claim 2 [[or 3]], wherein the compound which is capable of phase separation when combined with the polymer capable of forming a hydrogel is polyethylene glycol.

16. (original): The method of claim 1, wherein the aqueous dispersed phase comprises about 5 to 60 wt.-% polymer or prepolymer, and about 1 to 30 wt.-% bioactive protein.

17. (original): The method of claim 1, wherein the emulsion comprises an aqueous continuous phase, said aqueous continuous phase comprising a compound which is capable of phase separation when combined with the polymer capable of forming a hydrogel, and water, which compound is preferably polyethylene glycol.

18. (original): The method of claim 1, wherein the step of forming the emulsion comprises the substeps of:

(a) providing the bioactive protein in a solid, soluble form; and

(b) combining the bioactive protein with an amount of water.

19. (original): The method of claim 18, wherein the amount of water is selected to yield a concentration of the bioactive protein which is about equivalent to, or higher than the concentration of the bioactive protein in the dispersed phase of the emulsion.

20. (currently amended): The method of claim 18 [[or 19]], wherein the amount of water is provided in form of an aqueous solution or dispersion of a compound which is capable of aqueous phase separation when combined with the polymer capable of forming a hydrogel.

21. (currently amended): The method of ~~any of claims 18 to 20~~ claim 18, wherein the bioactive protein is provided in ~~lyophilised~~ lyophilized form.

22. (currently amended): The method of ~~claim 18 to 21~~ claim 21, wherein the bioactive protein is provided as a ~~lyophilised~~ lyophilized mixture comprising the polymer capable of forming a hydrogel.

23. (currently amended): The method of ~~any of claims 18 to 22~~ claim 18, wherein the bioactive protein is provided as a soluble precipitate.

24. (currently amended): The microspheres obtainable by the method of ~~any of the preceding claims~~ claim 1.

25. (original): Controlled release microspheres comprising a biodegradable, physically or chemically crosslinked polymer and a bioactive protein, being substantially free from insoluble aggregates of said bioactive protein.

26. (currently amended): The microspheres of claim 24 [[or 25]], wherein the crosslinked polymer is derived from a polysaccharide~~, and preferably from a dextran or dextran derivative~~.

27. (currently amended): The microspheres of ~~claims 24 to 26~~ claim 24, comprising about 0.1 to 60 wt.-% bioactive protein.

28. (currently amended): The microspheres of ~~any of claims 24 to 27~~ claim 24, wherein a fraction of at least about 95 wt.-% of the bioactive protein is dissolvable and releasable from the microspheres under physiological conditions.

29. (currently amended): The use of the microspheres of ~~any of claims 24 to 28~~ claim 24 as carriers for therapeutic or diagnostic bioactive proteins.

30. (currently amended): ~~Pharmaceutical~~ A pharmaceutical composition for the controlled release of a bioactive protein, comprising the microspheres of ~~any of claims 24 to 28~~ claim 24.

31. (currently amended): The composition of claim 30, ~~being~~ provided in dry and sterile form.

32. (currently amended): The composition of claim [[31]] 30, ~~being~~ formulated and processed to be suitable for parenteral injection.

33. (currently amended): The composition of claim 32, wherein the microspheres have an average diameter of about 1 μm to about 100 μm, as determined by laser diffraction.

34. (currently amended): The composition of claim 30, ~~being~~ formulated and processed to be suitable for inhalation.

35. (currently amended): The composition of claim [[35]] 34, wherein the microspheres have an average diameter of about 1 μm to about 20 μm, ~~and more preferably of about 2 μm to about 10 μm,~~ as determined by laser diffraction.

36. (currently amended): The composition of claim 34 [[or 35]], wherein at least about 80 wt.-% of the microspheres have a diameter between about 2 μm and 10 μm, as determined by laser diffraction.

37. (new): The microspheres of claim 24, wherein the crosslinked polymer is derived from a dextran or dextran derivative.